REMARKS/ARGUMENTS

Claims 1-29, 33-66, and 81 are active in this application.

Support for the amendment to Claim 1 is found in Claim 81 and page 6, lines 8-9 of the specification. Support for the amendment to Claim 1, Claim 66 and Claim 81 defining the second type 1 inflammatory response promoting agent is found in Claim 29 as originally filed and the specification on page 4, lines 21-26

Claim 22 and the specification on page 17 are amended to correct a typographical error of the agent GCP2, i.e., granulocyte chemotactic protein-2. Support for the fact that this simply corrects a typographical error is found in the knowledge in the art, which is exemplified by the attached PubMed protein database printout for GCP-2 (Locus: A54188).

The remaining amendments are provided to improve readability and for clarity.

No new matter is believed to have been added by these amendments.

INTERVIEW SUMMARY

Applicant thanks Examiner Canella for the in-person discussion held on October 21, 2004 and for a subsequent telephone discussion regarding the claimed invention and the publications cited in the Office Action. During this discussion, differences between these cited publications and the claimed invention were discussed, in particular, the publication of Yu.

In addition, Applicant thanks Examiner Canella and Supervisory Patent Examiner Siew for the courtesy of discussing this application and reviewing proposed amendments to the claims on December 20, 2004 with the undersigned and the Applicant on the telephone. During this discussion, it was agreed that in light of the amendments the rejection under 35 U.S.C. § 102(e) would be withdrawn.

With respect to the rejections under 35 U.S.C. § 103, Applicant explained why Yu combined with the remaining cited references fail to describe the local administration of the

antigen releasing agent, leukocyte attractant, and type-1 inflammatory response promoting agents as claimed. In addition, attention was drawn to the description in Yu where the goal of the invention described therein was to create a coagulated and crosslinked mass of cells and proteins to act as a retention environment for anti-neoplastic agents. It was further explained that the data presented in Yu, i.e., in Figure 3, do not support any localized immune response to the tumor given the fact that the treated tumor grows at the same rate as the control tumor.

The Examiners suggested amending the claims to define the combination of type-1 inflammatory response agents in the claimed method, for example, as on page 4 of the application to address obviousness rejections. Accordingly, the independent claims of the present application, i.e., Claims 1, 66, and 81, have been amended to define the second IR1 promoting agent inclusive of TNF-b as well as IL2, IL12, TNF-a, and mixtures of these.

It is the Applicant's understanding that the Examiners agreed that the cited prior art failed to describe or suggest the claimed invention and indicated that the rejections under 103, now of record, would likely be withdrawn in view of the deficiencies of the prior art.

The substance of the discussion and the rejections of record are discussed in more detail below.

THE REJECTION UNDER 35 U.S.C. § 102(e)

Applicant notes that Claim 83 has been cancelled. Accordingly, withdrawal of the rejection under 35 U.S.C. § 102(e) in view of Yu is requested.

THE REJECTIONS UNDER 35 U.S.C. § 103 (a)

Various combinations of the pending claims have been rejected under this title in view of the combination of Yu, Nishimura, Cameron, and Ferrero and then further in view of

(1) Rovere, Mollinedo, and Boggs; (2) Sager; (3) Garcia-Zepeda; (4) Wang and Ausubel; (5) Cerami and DeSanctis; (6) Semple; (7) Rovere, Monllinedo, Boggs, Aker, and Johnston; (8) Bottomly (9) Grooten; (10) Tuting; and (11) "what is recognized in the art" (pages 21 and 22 of the Official Action).

All of these rejections are unsustainable for the following reasons.

The combination of Yu, Nishimura, Cameron, and Ferrero fails to describe or provide a suggestion for the claimed invention. During the above-noted discussion, the Examiner clarified the basis for the obviousness rejections stating:

> The examiner additionally notes that the Yu reference was relied upon for teachings on the intra tumoral administration of relatively simple yet unspecific agents that act by direct contact with cells and the remaining prior art references were relied upon for teaching the obviousness of raising a TH1 immune response. (Interview Summary dated October 21, 2004).

However, this combination of publications does not suggest how to treat tumors by inducing a type 1 inflammatory response in a solid tumor involving the local administration of an antigen releasing agent, leukocyte attractant whereby leukocytes are induced to infiltrate the tumor, and agents to induce a type 1 inflammatory response in the tumor.

Yu's primary goal is to induce coagulation of the tumor with coagulation agents, oxidizing/reducing agents, and protein denaturants ([0009] page 1 of Yu). The result of this is a mass of tumor cells with proteins that are crosslinked to each other and reduces the tumor size (tumor burden) so that subsequent conventional cancer therapies have a smaller tumor to fight (see [0010], page 1 and [0019], page 2). Yu goes on to describe numerous possible options for administering conventional therapeutic agents that may stimulate an immune response or which directly attack the tumor itself, e.g., radiotherapy ([0010], page 1).

The Examiner citing [0019] of Yu states that "Yu teaches that the area of inflammation attracts lymphocytes and other inflammatory response mediators to the target

tumor site, and that said lymphocytes are exposed to tumor antigens released by the coagulated cells as the target tumor site, thus eliciting tumor specific immune responses." (see page 8 of the Official Action). Certainly that is what Yu states in [0019], however, the data in Yu do not support this statement. Specifically, the Examiner's attention is drawn to Figure 3 and the accompanying text in [0246].

It is noted that the growth rate of each curve is the same - meaning there is no difference between the treated group and the immunotreated group. Furthermore, there is no shrinkage of the tumor as a function of time, i.e., the tumors keep growing in size at the same rate and at day 8 the tumors have tripled in volume. The 50% difference in volume between the treated and non-treated tumors is caused by the treatment with ethanol which dehydrates the tumors and kills over 50% of the cells at the beginning (see [0055] and [0060] of Yu). This reduced starting volume is accountable and consistent in function of time but there remains a continuous growth in size. If, in fact, there was an immune response as the Examiner has alleged then the treated tumor would grow more slowly than the untreated control tumor. However, this is not what Yu's data show.

The Examiner has recognized that "Yu does not specifically teach the induction of a type 1 inflammatory response, or the inclusion of a chemokine for purpose of attracting leukocytes, although Yu teaches that the coagulum itself attracts lymphocytes." (page 9 of the Official Action). For the induction of a type 1 inflammatory response, the Examiner relies on Nishimura, Cameron, and Ferrero. These additional publications will be discussed below but before doing so, Applicant respectfully notes that the Examiner's characterization of Yu is incorrect.

There is nothing in Yu which provides any explanation as to how a local immune response to a tumor would occur. Coagulating a tumor would, in fact, not facilitate the induction of an intratumoral inflammation response. First, there is a need to have live

leukocytes in the local area of the tumor, which would not happen following Yu's teachings because the cells are fixed and killed by the ethanol. Second, these live leukocytes react on the injury by secreting chemotactic proteins. Those will travel through the blood vessels and create a chemotactic gradient. Circulating leukocytes migrate to the site of injury by sensing the chemotactic gradient and migrating along the gradient until they reach the injured site (see, for example, Ferrero cited in this rejection supporting the point that chemotactic factors enhance the ability of TILs to migrate to the extracellular matrix). This cannot happen if the local cells are being killed along with fixation and denaturation of the proteins and blood vessels in the local environment of the tumor, as in Yu. As a result, following the teachings of Yu there would be no chemotactic gradient that can be produced under these conditions to link the inside of the tumors with the outside immune system through the blood vessels and thus there is no infiltration and inflamation that can be initiated. This is, in fact, confirmed by the data presented in Yu's Figure 3 showing no immunotherapeutical effect, i.e., the growth of the treated tumor progresses at the same rate as the control, untreated tumor.

Furthermore, one reading Yu's disclosure would recognize this point as well, i.e., to cause a mass of denatured and coagulated cells minimally accessible, if at all, to the circulatory system. Specifically, attention is directed to [0059] of Yu wherein the advantage of the described invention is to create an environment to retain agents (emphasis added):

> This combination treatment is **advantageous because coagulation enhances retention of the anti-neoplastic agents within the coagulated neoplastic mass**, thereby exposing the neoplastic mass to the anti-neoplasm agent for longer time. In this aspect, coagulation acts as a controlled drug-release vehicle.

Yu simply provides no guidance as to the requirements after antigen release to induce a local type 1 immune response and is also in conflict with Yu's description and data that the tumor is transformed into a retention center. That raises the question--How can the tumor release antigens and be a center for retaining agents at the same time? It cannot.

One would not simply modify the described advantage, in Yu, of creating a retention environment and do something entirely different to permit the induction of a type 1 inflammatory response because modifying Yu in this way would render the Yu invention unsatisfactory for the intended purpose. (see MPEP 2143.01). Therefore, even if one combined the teachings of Nishimura, Cameron, and Ferrero with Yu one would not have the necessary direction to induce a type 1 inflammatory response in a solid tumor as presently claimed.

Nishimura describes the advantages of Th-1 dominant immunity and specifically describes inducing Th1 cells ***in vitro*** using IL-12 expressing B lymphoma cells (page S54, col. 2 and page S53 col. 1); inducing Th1-dominant immunity by administering α-galactosylceramide **intravenously** (see the paragraph bridging page S53); and inducing Th1-dominant immunity by dendritic cell-based vaccination in an ***in vitro*** **culture system** (S 53, col. 2 and S56, col. 2).

Cameron describes the assessment of combination approaches for tumor therapy by employing IL-2 irradiation and *in vitro* cultured Tumor Infiltrating Lymphocytes (TILs) in the presence of IL-1 (page 250: "TIL"). Cameron also describes local irradiation in the regions of the liver (page 250: "Local Irradiation"). The TILs were administered **intravenously** and the IL-2 was administered **intraperitoneally** (see page 251: "Immunotherapy Model").

Ferrero describes that tumor cells may enhance the release of chemotactic factors which facilitated TIL migration in the extracellular matrix (Abstract). All of Ferrero's experiments are performed *in vitro*.

It is noted that a specific element of establishing obviousness under 35 U.S.C. § 103 is that "the prior art reference (or references when combined) must teach or suggest all the claim limitations." (see MPEP § 2143). In view of the above, the combination of

publications fails to describe the local administration of antigen-releasing agent, leukocyte attractant, and a type 1 inflammatory response promoting agent to induce a type 1 inflammatory response as presently claimed. Specifically, Nishimura, Cameron, and Ferrero each describe *in vitro* experiments, intravenous administration, or intraperitineoul administration whereas Yu describes the local administration of coagulants, denaturants, and oxidizing agents to create a retentive area that does not stimulate a local type 1 immune response (again referring to Fig.3 of Yu and the explanation provided above). Thus, in combination, the cited publications fail to provide the requisite description for the local administration of agents as set forth in the claimed invention. Without this description in the prior art, the rejection is unsustainable.

As a second point, it is noted that an additional requirement to establish obviousness under 35 U.S.C. § 103: "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference the teachings. . ." (see MPEP § 2143). Specifically, Nishimura, Cameron, and Ferrero do not suggest modifying Yu to locally administer agents. In fact, one reading Yu (and Nishimura, Cameron, and Ferrero) would not do so because as explained above, Yu's goal is to create an environment that enables the retention of agents not the release of agents from the tumor site to attract the necessary components for mounting a type-1 inflammatory response, once again referencing MPEP 2143.01).

Accordingly, the claimed invention would not have been obvious in view of the cited publications of Yu combined with Nishimura, Cameron, and Ferrero.

Withdrawal of this ground of rejection is therefore requested.

Furthermore, the remaining publications cited in the various rejections under 103 do not remedy the core deficiencies of the combination of Yu, Nishimura, Cameron, and Ferrero and therefore the remaining rejections under 35 U.S.C. § 103(a) are also unsustainable.

Each of the remaining publications describes that certain sub-embodiments or specific agents were allegedly known in the art. However, the combinations of cited publications fail to provide the requisite description for the local administration of agents to treat tumors and/or induce a type 1 immune response as set forth in the claimed invention.

Therefore, Applicant requests withdrawal of the rejections under 35 U.S.C. § 103(a) based on the combination of Yu, Nishimura, Cameron, and Ferrero further in view of (1) Rovere, Mollinedo, and Boggs ; (2) Sager; (3) Garcia-Zepeda; (4) Wang and Ausubel; (5) Cerami and DeSanctis; (6) Semple; (7) Rovere, Monllinedo, Boggs, Aker, and Johnston; (8) Bottomly (9) Grooten; (10) Tuting; and (11) "what is recognized in the art."

THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The rejection of Claim 56 under 35 U.S.C. §112, first paragraph is respectfully traversed.

In this rejection, the Examiner alleges that no guidance is provided in the specification to support the limitation of Claim 56, i.e., administering a memory cell-inducing agent after the tumor shrinks to less than 10 percent of its size immediately prior to administration of the memory cell agent. Applicant disagrees. In particular, attention is directed to Example 1 beginning on page 24 of the present specification which gives a detailed outline concerning the administration of agents to achieve the shrinkage of the tumor size to less than 10 percent of its size (see page 25, lines 17-18 as well). Accordingly, the specification provides sufficient guidance for one to practice the method claimed in Claim 56 without undue experimentation.

Withdrawal of this ground of rejection is requested.

THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The majority of the rejections of Claims 1-66, 81 and 83 under 35 U.S.C. §112, second paragraph have been addressed by amendment. Specifically, Applicant notes the following.

Claim 83 is cancelled.

Claims 1, 66, and 81 have been amended to define a first and second IR-1 promoting agent.

The term "strong" has been deleted from Claim 3.

As noted above, Claim 22 has been amended to correct the spelling of GCP-2 has been correct to granulocyte chemotactic protein -2, which is an art recognized term.

Concerning Claim 37, the lymphocyte attractant administered can be either or both a second dose administered in iia) and/or to further elicit infiltrating leukocytes as in iia). Therefore, the claim adds an additional administration from Claim 1, i.e., further comprising, as thus further limits Claim 1.

Concerning Claim 38, which is dependent from Claim 37, Applicant notes the following. Claim 1 refers to leukocyte whereas Claim 37 refers to lymphocyte. Claim 38 since it is dependent from Claim 37 also refers to lymphocyte and defines several options of the lymphocyte attractant. Therefore, it is clear to which claim and to which attractant Claim 38 is further limiting.

Claim 39 is amended to clarify that two attractants are administered and that those two attractants are IP-10 and Mig.

Claims 46, 47 and 48 have been amended to remove the phrase "independently selected."

In view of the above, withdrawal of this ground of rejection is requested.

THE OBJECTION OF CLAIM 24

The objection to Claim 24 based on a spelling issue of "eotaxin" is unsustainable. In fact, "eotaxin" is spelled correctly in Claim 24 of record and as submitted in the listing of claims herein. Further support for the fact that "eotaxin" is the correct term is found in the attached publication of Palframan et al (Blood, 91(7):2240-2248 (1998)).

Allowance of this application is requested. Early notice of such allowance is also requested.

Respectfully submitted,

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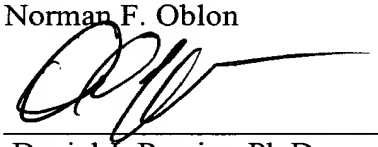

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